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Is parathyroid hormone measurement useful for the diagnosis of renal bone disease?

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The non-invasive diagnosis of bone turnover in patients with chronic kidney disease (CKD) remains difficult compared with bone histomorphometry as the gold standard. Most clinicians rely on surrogate markers, mainly serum parathyroid hormone and total alkaline phosphatases, in association with serum calcium and phosphorus. Although very high serum PTH levels generally allow the diagnosis of high bone turnover, slight elevations, normal, or low values cannot allow a reliable distinction between normal or low turnover.

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In the past decades, clinical nephrologists have become used to considering so-called 'intact' parathyroid hormone (PTH) a reliable surrogate marker for bone turnover in patients with chronic kidney disease and the associated mineral and bone disorder (CKD-MBD). Although many other circulating markers of bone turnover have been examined and proposed for diagnostic and therapeutic purposes in patients with CKD,[1] none of them has gained widespread acceptance in clinical routine.

The use of PTH as first choice for the characterization of normal versus pathologic bone in CKD was reinforced by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines on bone metabolism and disease in 2003,[2] which set circulating 'intact' PTH values for chronic dialysis patients with supposedly normal bone turnover at values between 150 and 300 pg/ml, that is, approximately two to three times higher than the upper limit of normal using Nichols Allegro immunoradiometric assay for 'intact' PTH (N-IRMA, no longer available). For CKD patients not yet on dialysis, the corresponding PTH target was arbitrarily set to somewhat lower values, in the absence of reliable data in the literature. This PTH guideline was issued despite voices of dissent questioning the validity of predicting bone turnover on the basis of these ranges of serum 'intact' PTH;[3] arguing that the serum PTH range reflecting normal bone turnover needed to be lower with another assay (B-IRMA) that measured not PTH fragments like the Nichols assay, but exclusively the whole PTH molecule;[4] and arguing that aluminum overload should be taken into account in the interpretation of the predictive value of any serum PTH measurement.[5] Other discordant findings were made in children and adolescents on long-term dialysis treatment. Intermittent calcitriol therapy given to these patients resulted, at least in some of them, in normalization of bone formation despite persistently elevated serum 'intact' PTH levels. Only in those patients who developed adynamic bone disease did the serum PTH decrease.[6]

The issue of the relationship between circulating PTH and bone turnover has gained an additional degree of complexity since the disappearance from the market of Nichols N-IRMA and the introduction of numerous other, presently available PTH detection assays. Most of them are of the so-called second generation, measuring 'intact' PTH, that is, both the whole PTH molecule and PTH fragments, with limited comparability from one assay to another.[7] Others measure 'whole' PTH (also called 'bio-intact' PTH) alone. None of the new assays has been validated with respect to bone biopsy findings. Hopefully, such validations will be reported in the near future.

Barreto *et al.*[8] (this issue) provide a breath of fresh air to the above voices of dissent. They decided to assess, in a cohort of patients undergoing intermittent hemodialysis in São Paulo, Brazil, to what extent the 'intact' PTH range of 150–300 pg/ml reflected normal bone turnover. They followed 97 patients for one year. They obtained a bone biopsy in each of them at baseline and a repeat biopsy in 64 of them 12 months later. The results obtained were incompatible with the K/DOQI recommended 'normal' 'intact' PTH range for CKD stage 5D patients. Two-thirds of those subjects whose baseline PTH was in that range had low-turnover bone disease on the basis of bone histomorphometry, and one in four had high-turnover bone disease. After one year of follow-up, the discrepancy between 'intact' PTH and bone biopsy findings was similar. Moreover, normalization of bone turnover was difficult to achieve even in those patients whose serum 'intact' PTH values could be maintained in the recommended K/DOQI range.

The question then arises of why Barreto *et al.*[8] failed to confirm the K/DOQI definitions of the optimal serum 'intact' PTH range for CKD stage 5D patients. There may be several reasons.

First of all, one could speculate that the Brazilian dialysis patients were different from those in Europe or North America. However, Ferreira *et al.* recently reported a similar dissociation between bone histomorphometry

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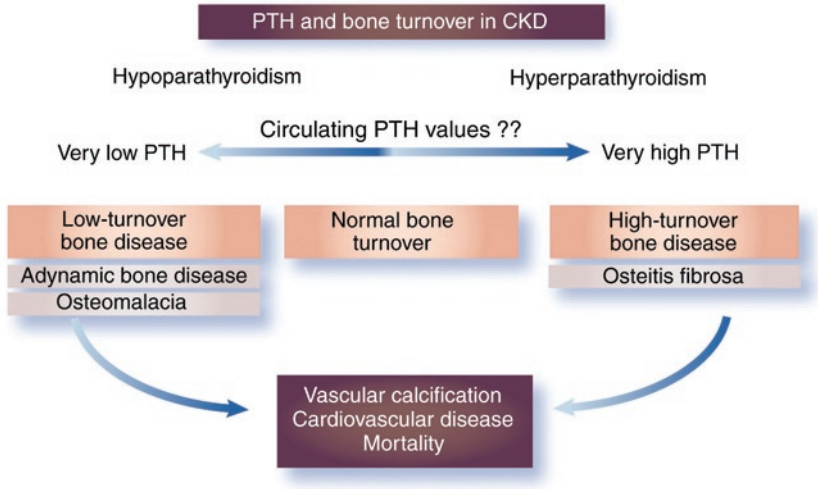

Figure 1 | PTH and bone turnover in chronic kidney disease.

findings and serum 'intact' PTH in a chronic hemodialysis patient cohort from Portugal.[9] They performed a randomized open-label study comparing the effects on bone histology of sevelamer hydrochloride with those of calcium carbonate at baseline, and again after one year of follow-up. Like Barreto *et al.*,[8] they found a high prevalence of low-turnover bone disease despite well-controlled serum calcium, phosphorus, and 'intact' PTH levels in the majority of the patients, according to K/DOQI criteria, both at baseline and after one year of follow-up, with serum 'intact' PTH levels mostly in the lower half of the recommended range in the calcium group and in the upper half or slightly above in the sevelamer group.

Second, the patients in the study by Barreto *et al.*[8] had a relatively high prevalence of aluminum overload on the basis of bone histology analysis, compared with the patients of many other such studies. This should have changed the relationship between serum PTH and bone histology findings, as aluminum intoxication could create a state of skeletal resistance to PTH, according to Fournier *et al.*[4] Barreto *et al.*[8] did not find a correlation of low-turnover bone disease with the presence of positive aluminum staining in their patient cohort, in contrast to obvious correlations with the traditional risk factors age and diabetes. Absence of correlation, however, does not necessarily imply absence of causation. It is noteworthy that 60% of their patients with low-turnover bone disease had strongly positive bone aluminum staining (aluminum bone surface/total bone surface >25%), compared with only 30% of their patients with high-turnover bone disease. Ferreira *et al.* observed the above-mentioned discrepancy between 'intact' PTH and bone histology in the absence of stainable bone aluminum greater than 20% at study start, but they did not report the proportion of patients with zero aluminum staining in their study.[9]

Third, Barreto *et al.*[8] used Immulite assay to measure 'intact' PTH, in contrast to previous studies, which most often used Nichols N-IRMA. According to Souberbielle *et al.*,[7] 'intact' PTH values obtained with Immulite assay present a positive median bias of 38% compared with N-IRMA. By a simple rule of 3, this would mean that, with the Immulite assay, both the lower and the upper serum PTH limits should have been set at somewhat higher values, roughly at a range of 210–410 pg/ml, although it is difficult to adjust values obtained with one assay to those obtained with another assay. Barreto *et al.*[8] say that they nevertheless made such an adjustment; this should have slightly reduced the number of patients with low-turnover bone disease who had 'intact' PTH levels above the upper limit of this adapted range, although a substantial number among them would still have been erroneously misclassified as having high-turnover bone disease on the basis of Immulite PTH measurement alone.

Fourth, Barreto *et al.*[8] used reference ranges for dynamic parameters of bone histomorphometry that were established in a control population of North America, with possibly a higher degree of vitamin D insufficiency and higher serum PTH levels than in the general population of the São Paulo area in Brazil. If so, this would have shifted the lower range of normal bone turnover toward somewhat higher levels than it would have been with local controls. This in turn could have led to a certain overestimation of the prevalence of low bone turnover in the dialysis patients studied by Barreto *et al.*[8]

Finally, a number of actors other than PTH play a role in the regulation of bone formation and resorption. We already have mentioned age and diabetes. One has to add further the influence of numerous endogenous and exogenous factors. Among the former, several hormones, growth factors, and cytokines have been shown to modulate bone turnover.[10] Among the latter, the administration of excessive amounts of aluminum-containing phosphate binders, calcium-containing compounds, and/or active vitamin D derivatives has long been known to reduce bone turnover.

Where do these recent studies on the complex relations between serum 'intact' PTH and bone histology lead us? The widely accepted association between circulating PTH values and the type of renal osteodystrophy will have to be redefined, as suggested in Figure 1, with probable differences from one PTH assay to another. In the future, reliable bone-derived markers of bone formation and resorption probably will replace 'intact' PTH as the main surrogate marker for bone turnover in patients with CKD. The claim that third-generation 'whole' (or 'bio-intact') PTH assays may have a higher predictive value than 'intact' PTH assays for the differential diagnosis between low- and high-turnover bone disease states

needs to be confirmed by future direct confrontations with bone biopsy findings. Ideally, invasive methods such as bone biopsy should be replaced by a combination of biochemical markers and highly performing imaging techniques for an optimal assessment of bone structure and function, the prediction of fractures, and adequate treatment and prevention.

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